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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/690.775	08/01/96	FELDMANN	M KIR92-01A4

EXAMINER

18M1/0303

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ART UNIT	PAPER NUMBER
1806	6

DATE MAILED: 03/03/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 12/9/96

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-31 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☐ Claim(s) 1-31 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. The filing date of the instant claims is deemed to be the filing date of parent application USSN 08/690,775, i.e. 8/1/96. Priority application USSN 08/403785 and PCT/GB94/00462 do not support the broader claims of the instant application, including "preventing a tumor necrosis factor-mediated disease", "preventing Crohn's disease", "tumor factor-mediated disease", "binds to one or more amino acids of hTNFα selected from the group consisting of about 87-108 and about 58-80", "cA2" and "epitope of cA2" . If applicant desires priority prior to 8/1/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

3. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

The use of trademarks have been noted in this application. A TRADEMARK should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The specification is objected to and claims 1-32 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs can be species- and model-dependent, it is not clear that reliance on the clinical treatment of rheumatoid arthritis with multiple infusions with the anti-TNF antibody cA2 and methotrexate for rheumatoid arthritis accurately reflects the relative efficacy of any anti-TNF antibody or anti-TNF specificity as well as targeting any TNF-mediated diseases encompassed by the claimed methods and compositions.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Although in vitro experimental studies and animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In vitro assays are conducted under controlled conditions which do not necessarily reflect the complexity of in vivo conditions. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Often the antagonist and the stimulus/insult are given at the same time. Immunosuppression is much easier to achieve under such controlled conditions that experienced in the human immunoregulatory diseases such as the acute and chronic immune diseases, autoimmune diseases, inflammatory diseases and neurodegenerative diseases targeted by the claimed invention. In human diseases, patients are treated generally after the onset of disease and not prior to disease.

There is insufficient information or guidance as to how to select those patients to "prevent" the onset of the various diseases encompassed by the claimed invention. There is insufficient information to determine which markers would be predictive of said diseases in order to treat patients prior to the onset of said diseases, as a preventive regimen.

Elliott et al. (Arthritis and Rheumatism, 1993) disclose that the appropriate specificity for treating arthritis is TNFα and not TNFβ (see Introduction in particular). Therefore, not all TNFs nor all TNF specificities would be appropriate to target even for the instant exemplified results in arthritis, much less with the breadth of diseases encompassed by the claimed methods. There is insufficient information or nexus for targeting any TNF specificity to treat the breadth of TNF-mediated diseases encompassed by the claimed methods.

Natanson et al. (Ann Int Med., 1994) teach that anti-TNF was not beneficial in sepsis and septic shock and that targeting TNF could be harmful (see Anticytokine Therapies).

Furthermore, there is insufficient guidance and direction as to the selection and enablement of any TNF antagonist.

Therefore, it is not clear that the skilled artisan could predict the efficacy of targeting any TNF-mediated disease or inflammatory disease with any TNF specific antibody and methotrexate. It is important to note that there are distinct differences in the cytokine requirements for particular types of inflammation Applicant has not provided sufficient information or nexus information a priori that establishes the efficacy of the claimed invention for the treatment of any TNF-mediated disease by targeting any TNF. The specification does not teach how to extrapolate data obtained from anti-

TNFα and methotrexate on arthritis to the development of effective in vivo human therapeutic methods and compositions for any TNF-mediated diseases, commensurate in scope with the claimed invention.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective anti-inflammatory therapies with anti-cytokine therapy commensurate in scope with the claimed methods and compositions, undue experimentation would be required to practice the claimed methods and compositions with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and compositions and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting any TNF-mediated disease and preventing TNF-mediated disease with any TNF-specific antibody.

7. The specification is objected to and claims 8, 9, 16-17, 24-25, 29-30 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

It unclear if a cell line which produces an antibody having the exact structural and chemical identity of cA2 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species cA2. Deposit of the appropriate cell line would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Satisfying the deposit requirement set forth above for the cA2 would satisfy enablement of the this particular biological species under 112, first paragraph. However, it is noted that applicant also incorporates by reference information on the cA2 to other USSN not listed as priority documents. See page 14 of the instant specification. If such information is essential matter, then applicant is reminded of the following.

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. *Ex parte Schwarze*, 151 USPQ 426 (Bd. of Appeals, 1966). an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See *In re Fouche*, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

8. Claims 1-3, 8, 16, 24, 29 and 31 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-3 are indefinite in the recitation of "tumor necrosis factor-mediated disease" because the characteristics of said diseases are ill-defined and ambiguous. It is not clear whether said diseases reads on any inflammatory condition wherein TNF is present, wherein TNF has a direct role in pathology or wherein TNF has an indirect role in pathology. Although TNF contributes to certain conditions associated with inflammatory diseases, an artisan would not necessarily classify these diseases as TNF-mediated diseases, but rather inflammatory diseases wherein TNF plays some role.

These claims are further ambiguous in the recitation of TNF since there are different members associated with TNF, and it is not clear whether any disease with any role played by any TNF falls into the metes and bounds of "TNF-mediated disease". Applicant should consider amending the claims to specific diseases or inflammatory diseases, where appropriate.

For the reasons set forth above in section 7, there is insufficient guidance and direction as to enable the breadth of treating any TNF specificity in order to treat any "TNF-mediated disease" or inflammatory disease encompassed by the instant claims. In addition, there is insufficient direction and guidance as how to determine whether any TNF or a particular TNF mediates a disease and how critical a role any TNF or a particular TNF has to the diseases encompassed by the claimed invention.

B) Claim 31 is indefinite in the recitation of TNF "antagonist" because the characteristics of the "antagonist" are not known. This language is vague and indefinite since it encompasses potentially thousands of different antagonists and it is not apparent from the disclosure which particular antagonists are being referred to. These "antagonists" could be any protein or non-protein molecule that interferes with TNF either in a direct or indirect manner, both known and unknown.

There is insufficient direction or guidance provided to assist one skilled in the art in the selection of such "antagonists" nor is there evidence provided that such "antagonists" would be effective in inhibiting TNF either in vitro or in vivo, for the reasons set forth above in section 7. It would require undue experimentation to produce all such possible antagonists without more explicit guidance from the disclosure. It would require undue experimentation to investigate all such antagonists. It appears that undue experimentation would be required of one skilled in the art to practice the claimed method using the teaching of the specification alone.

C) Claims 8, 16, 24 and 29 are indefinite in the recitation of "binds to the epitope of cA2" because it is unclear whether the specificity is cA2 or to the particular epitope bound by cA2. Further, it is unclear whether this refers to a specific antigenic determinant or the intention is for an antigen. The characteristics of said epitopes are ambiguous and ill-defined. In addition to linear sequences, epitopes may be conformation dependent and discontinuous, particularly with antibodies. However, applicant has not define or set forth the metes and bounds of said recognized epitopes.

Further, antibodies that can inhibit the binding of the claimed antibody species may block said binding or other functional attributes via steric hindrance as well as via binding the same epitope. In addition, the claims recite "the epitope" which implies there is a particular epitope intended and antibodies can recognize more than one epitope. These phrases also read on small amino acid sequences encompassed by linear or conformational epitopes which are incomplete regions of the epitopes bound by the claimed TNF-specific antibodies. There is insufficient guidance to any or all of the myriad antibodies that can bind an epitopes encompassed within this language; since the antibodies could bind either conformational or linear sequences as well as glycosylated epitopes; the antibodies are apparently determined by blocking assays which could indicate both steric hindrance and direct binding of the same epitope; and the antibodies could block only portions or irrelevant cross-reactive epitopes. One of the skill in the art would neither expect nor predict the appropriate functioning of the antibodies as broadly claimed. Applicant has only provided guidance as to the particular cA2-specific antibody species and not to the exact nature of the epitope bound by the claimed antibody

species. It would require undue experimentation to determine said epitopes without clearly defining the metes and bounds of said epitopes.

D) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

9. Claims 1-31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-6, 10-14, 18-22, 26-27 and 31 are indefinite in "tumor necrosis factor" because there are different members of this genus and it is not clear which TNF is intended.

B) Claims 7, 15 and 23 are indefinite in the recitation of "about 87-108 and about 59-80" because it is unclear what these numbers refer to. Applicant should amend the claims to recite that these are amino acids residues and incorporate the appropriate SEQ ID NOS. to clearly define the appropriate specificity.

C) Claims 8, 9, 16, 17 ,24, 25, 29 and 30 are indefinite in the recitation of "cA2" because its characteristics are not known. The use of "cA2" as the sole means of identifying the claimed biological species renders the claim indefinite because "cA2" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct products.

D) Claim 28 is indefinite in the recitation of "hTNFA" because "hTNFα" is appropriate term for clarity and consistency; otherwise "hTNFA" is ambiguous and confusing as to its intended specificity.

The amendments must be supported by the specification so as not to add any new matter.

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

11. Claims 1-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Bender et al. (U.S. Patent No. 5,317,019) in view of Elliott et al. (Arthr. Rheum., 1993; 1449, #AS3), Elliott et al., (Lancet , 1994; 1449, #AT3), Flesch et al. (Blood, 1992), Barrera et al. (Cytokine, 1991) and Kozarek et al. (Ann. Int. Med., 1989).

The instant claims are drawn to methods and compositions comprising methotrexate and TNF-specific antibodies.

Bender et al. teaches the use of TNF antagonists in the treatment of a number of TNF-mediated inflammatory conditions, including arthritis and Crohn's disease encompassed by the claimed methods. Bender et al. differs from the instant claims by not using TNF-specific antibodies and methotrexate to treat said TNF-mediated inflammatory conditions.

Elliott et al. teach the treatment of arthritis with chimeric monoclonal antibodies to TNF, including the instant cA2 specificity (see entire document). The cA2 specificity was drawn to the claimed antibody specificities.

Flesch et al. teaches the treatment of GVHD, which includes a number of lesions including skin and the gut with TNF-specific antibodies (see entire document).

Barrera et al. teaches the use of methotrexate including suppressing the production of TNF in arthritic patients (see Abstract).

Kozarek et al. teach the use of methotrexate as an anti-inflammatory agent on inflammatory bowel disease (see entire document).

The claimed timing of administration and effective dosages were well known in the art, as the ordinary artisan would have applied therapeutic manners to achieve the therapeutic endpoint of diminishing inflammatory conditions.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as methotrexate. Combination therapies were well known in the art and both methotrexate and anti-TNF antibodies were shown to be effective in vivo. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. No claim is allowed.

12. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
March 3, 1997